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Gluconic acid promoted cascade reactions of 2-phenylimidazo[1,2-a] pyridine-3-carbaldehyde with cyclohexane-1,3-dione to create novel fused bisheterocycles

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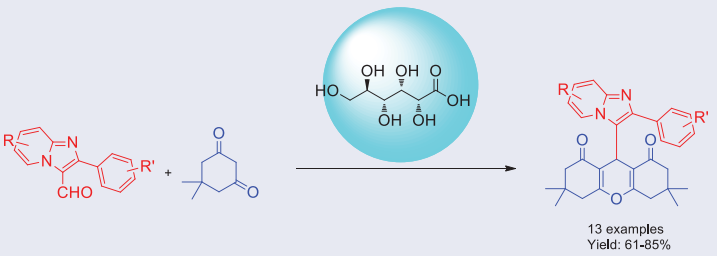
ABSTRACT

Here in, we described the synthesis of novel bisheterocycles imidazopyridine bearing xanthenedione by reacting various substituted 2-phenylimidazo [1,2-a] pyridine-3-carbaldehyde with cyclohexane-1,3-dione in gluconic acid aqueous solution (GAAS) via a tandem Knoevenagel followed by Michael, cyclization & tautomerization sequence. The use of GAAS in organic synthesis offers significant benefits like cost-effective, simple operation, reusable catalyst and green method. The reaction completed in 2–12 h to afford white stable solid compounds with very good yield. The structures of the compounds are confirmed by analyzing MS, IR, ^{1}H NMR and ^{13}C NMR spectra. Further, the structure of compound 3 h was confirmed by XRD analysis.

GRAPHICAL ABSTRACT



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Introduction

Nowadays, there is an increasing demand for the environmentally benevolent methodology for the preparation of organic compounds since the use of conventional organic solvents pose a threat to the environment. In this direction, chemists are focused in designing and implementing green chemistry methodology by exploiting reactions in the natural based reagents and solvents that could improve the chemical process

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including reuse of the materials and reduction of generation of the hazardous products. One such natural based material is bio-based material which replaces the use of conventional organic solvents. These are ethyl lactate, glycerol, 2-methyl-tetrahydrofuran, δ-valerolactone, gluconic acid, carbohydrates-based low melting mixture, deep eutectic solvents, and ionic liquid have been reported as catalysts, eco-friendly, renewable, sustainable, and harmless material for the various types of organic transformation.[1–6] Interestingly, Gluconic acid aqueous solution (GAAS) has been projected as a green environmentally friendly substance that can act as catalyst & solvent. It is present in a natural product such as fruits, rice, dairy products, wine, meat, vinegar and honey and possessing various advantageous qualities like nonvolatile, biodegradable, low-cost, and recyclable. Several reports introduced GAAS as a promoting medium for many organic transformations.[7–10]

Bisheterocycles have shown improved pharmacological and many other properties in different areas such as chelation ability,[11] antibacterial,[12] antifungal,[13] and antidiabetic activity.[14] Bisheterocycles synthesis is gaining importance of synthetic community due to their potential applications.[12,15,16] In this context, xanthenedione and imidazo[1,2-a]pyridine scaffolds are important heterocycles that show many biological activities. For example, xanthenedione exhibit several biological activities such as antimicrobial,[13] anti-inflammatory,[17] anticancer,[18,19] antiviral,[20] antiplasmodial,[21] antihypertensive,[22] phototoxicity,[23] antagonist,[24] leishmanicidal,[25] antioxidant,[26] and acetylcholinesterase inhibition (AChE).[27] Besides these activities, its uses are also reported in luminescent sensor, laser technology, cosmetics, pigments, and in fluorescent materials.[28–30] Xanthene nucleus is also found in the natural product like allanxanthone C, oliganthins, funiculosone, and gaudichaudione.[31–34] Cyclohexanedione is an important part present in various compounds and displaying different biological profiles. There are a variety of cyclohexanedione based derivatives reported for a various activity such as plant growth enhancers,[35] antimalarial,[36] HPPD inhibitors with herbicidal activity [37–40], e.g. Cycloxydim, clethodim, and butroxydim.[40] 1,3-cyclohexanedione is one of the reactants needed for the synthesis of xanthenedione moiety.

Additionally, imidazo[1,2-a]pyridine is the main class of fused heterocycles which represent the key core of various natural products and pharmaceuticals.[41] Imidazo[1,2-a] pyridine derivatives exhibit various biological and pharmacological activities such as anti-inflammatory, anticancer, antiviral, antiosteoporotic, antiparasitic, BACE-1 inhibitors, acetylcholinesterase inhibitors, antihypertensive, antiviral, benzodiazepine and gamma-aminobutyric acid receptor agonists.[42–45] These types of molecules are also used in psychiatry and autoimmune disorders.[46] Imidazopyridine based drugs such as zolpidem, alpidem, olprinone, zolimidine, necopidem, saripidem, GSK812397, and rifaximin are used for the treatment of various types of disease.[47–50] Figure 1 represents some medicinally important molecules of imidazopyridine and xanthenedione based scaffold Based on such interest in heterocyclic chemistry, our research group is involved in the development of new synthetic protocols for the creation of novel bioactive heterocyclic molecules.[35,36,51,52] Therefore, we planned to synthesize bisheterocyclic imidazopyridine fused with xanthenedione moiety (Figure 1; synthetic target) in gluconic acid aqueous solution (50 wt %, GAAS).

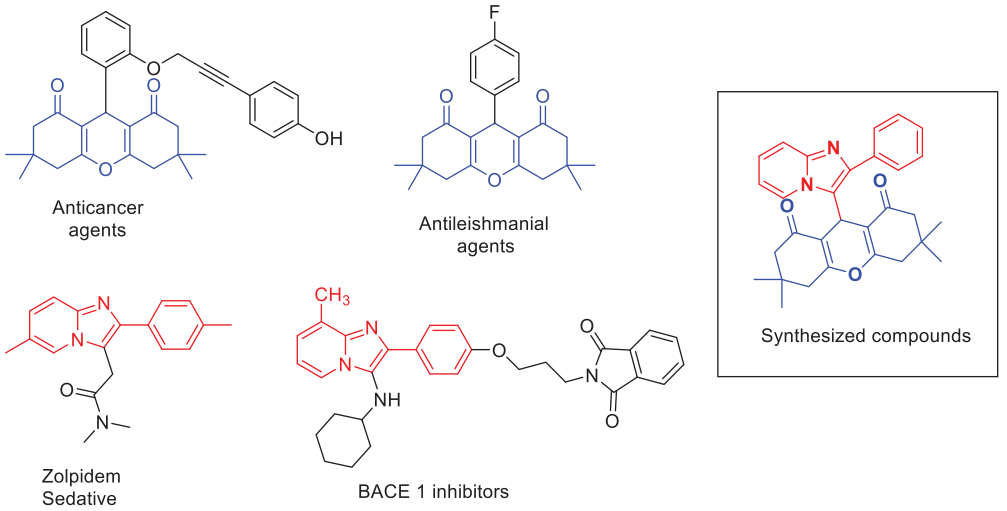
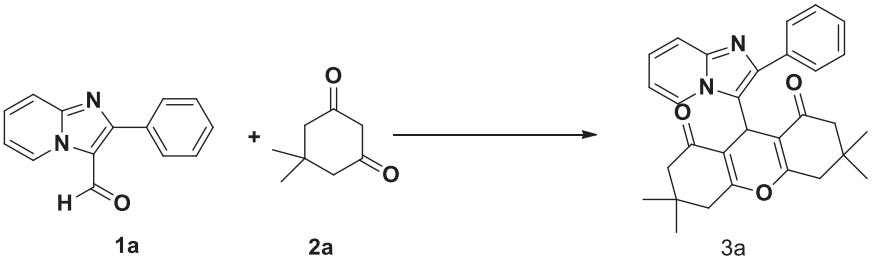


Figure 1. Biologically active imidazopyridine and xanthenedione based molecules.

Result and discussion

Synthesis of target molecule required a substituted 2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde which was synthesized by the reported procedures in two steps.[53] Then the reaction of various substituted 2-phenylimidazo [1,2-a]pyridine-3-carbaldehyde with various 1,3-cyclohexandione was carried out to obtain novel fused synthetic target. In order to find the optimized conditions, a model reaction was performed in different solvents including GAAS at various temperatures for the synthesis of the target molecule (3a) (Table 1). The reaction was monitored by TLC at various intervals of time for 12 h at room temperature (rt). The reaction was monitored via TLC in 80% ethyl acetate: hexane as the mobile phase and visualized under UV light at wavelength 254 nm. No reaction was observed in the case of solvents and gluconic acid at room temperature (rt) (Table 1: Entries 1 to 7). After this, the reactions were performed at 60, 80, and 100 °C in GAAS (Table 1: Entries 8–10). We observed trace product at 100 °C on TLC. Then, we tried a combination of GAAS and EtOH (1 ml each) at rt, 60, 80, and 100 °C. No product was obtained at room temperature (rt), followed by product formation under 60, 80, and 100 °C (Table 1: Entries 11 to 14). At 100 °C, 34% yield was obtained in 12 h (Table 1: Entry 14). After these encouraging results, further we increased the amount of GAAS from 1 ml to 7 ml and fixed the 1 ml EtOH volume for each reaction. The yield of the product was found to be increased with an increased amount of GAAS up to 5 ml and became constant in 6 ml and 7 ml GAAS in 12 h (Table 1: Entries 15–20). We monitored the reaction at various time intervals in reaction conditions (Table 1: Entry 18) and found that the reaction was completed in 2 h. TLC showed two spots, one was between dimedone and 2-phenylimidazo [1,2-a]pyridine-3-carbaldehyde and another spot was above the 2-phenylimidazo [1,2-a]pyridine-3-carbaldehyde. As reactions proceeded the spot above the 2-phenylimidazo [1,2-a]pyridine-3-carbaldehyde was disappeared with increase in intensity of spot between the 2-phenylimidazo [1,2-a]pyridine-3-carbaldehyde and dimedone, Figure 2 of supporting information. Therefore, the optimum reaction condition was 5 ml GAAS and 1 ml ethanol with 88%

Table 1. Optimization of reaction conditions[a].



1a 2a 3a

Entry	Solvent	Quantity	Temperature (°C)	Time (h)	[b]3a
1.	No solvent	–	rt	12	–
2.	Water	1 ml	rt	12	–
3.	Ethanol	1 ml	rt	12	–
4.	Methanol	1 ml	rt	12	–
5.	PEG–400	1 ml	rt	12	–
6.	Glycerol	1 ml	rt	12	–
7.	GAAS	1 ml	rt	12	–
8.	GAAS	1 ml	60	12	–
9.	GAAS	1 ml	80	12	–
10.	GAAS	1 ml	100	12	Trace
11.	GAAS + EtOH	1 ml each	rt	12	–
12.	GAAS + EtOH	1 ml each	60	12	18
13.	GAAS + EtOH	1 ml each	80	12	25
14.	GAAS + EtOH	1 ml each	100	12	34
15.	GAAS + EtOH	2 ml + 1	100	12	48
16.	GAAS + EtOH	3 ml + 1 ml	100	12	57
17.	GAAS + EtOH	4 ml + 1 ml	100	12	79
18.	GAAS + EtOH	5 ml + 1 ml	100	12/2	88/88
19.	GAAS + EtOH	6 ml + 1 ml	100	12	88
20.	GAAS + EtOH	7 ml + 1 ml	100	12	88
21.	GAAS + Water	5 ml + 1 ml	100	12	–
22.	GAAS + MeOH	5 ml + 1 ml	100	12	45
23.	GAAS + PEG-400	5 ml + 1 ml	100	12	45
24.	GAAS + Glycerol	5 ml + 1 ml	100	12	40
25.	[c]GAAS + EtOH	5 ml + 1 ml	100	2	82
26.	[d]GAAS + EtOH	5 ml + 1 ml	100	2	87

[a]Reaction condition: 1a (1.0 mmol) and 2a (2.0 mmol).
[b]Yield: Isolated yield after silica gel chromatography.
[c]Recovered GAAS third run.
[d]20 mmol scale.

yield in 2 hours. We checked the combination of GAAS with other solvents also. In all the combinations and reaction conditions, a product was obtained in varying yield in 12 h (Table 1: Entries 21–24).

The optimum reaction condition was further investigated for the substrate scope and the results obtained are summarized in Scheme 1. Various formylated imidazopyridines bearing electron withdrawing and electron donating groups were reacted with substituted/unsubstituted cyclohexane-1,3-dione to afford the required products (Scheme 1). The different functional groups bonded to imidazopyridines were stable in optimum reaction condition.

The effect of reaction time on the yield of the product was determined by carrying out a reaction at different intervals of time. The yield of the product was determined at 30, 60, 90, 120, 150, and 180 minutes. It was found that as time increased, the yield of the desired product increased upto 120 minutes and further the yield didn't increase at

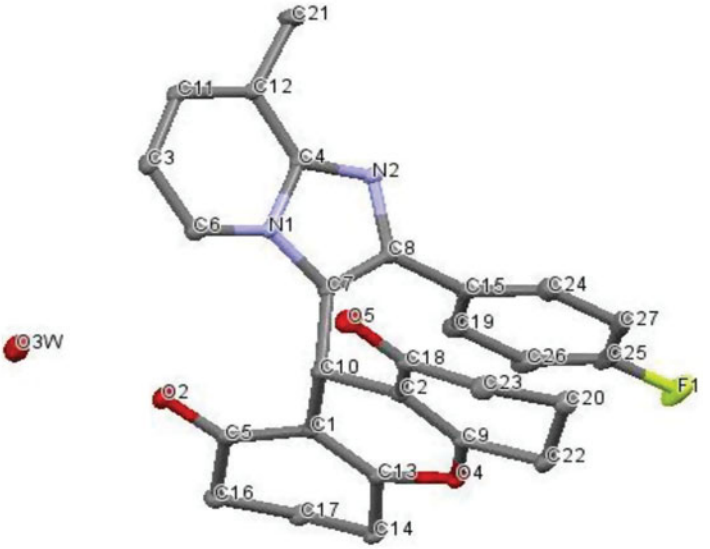


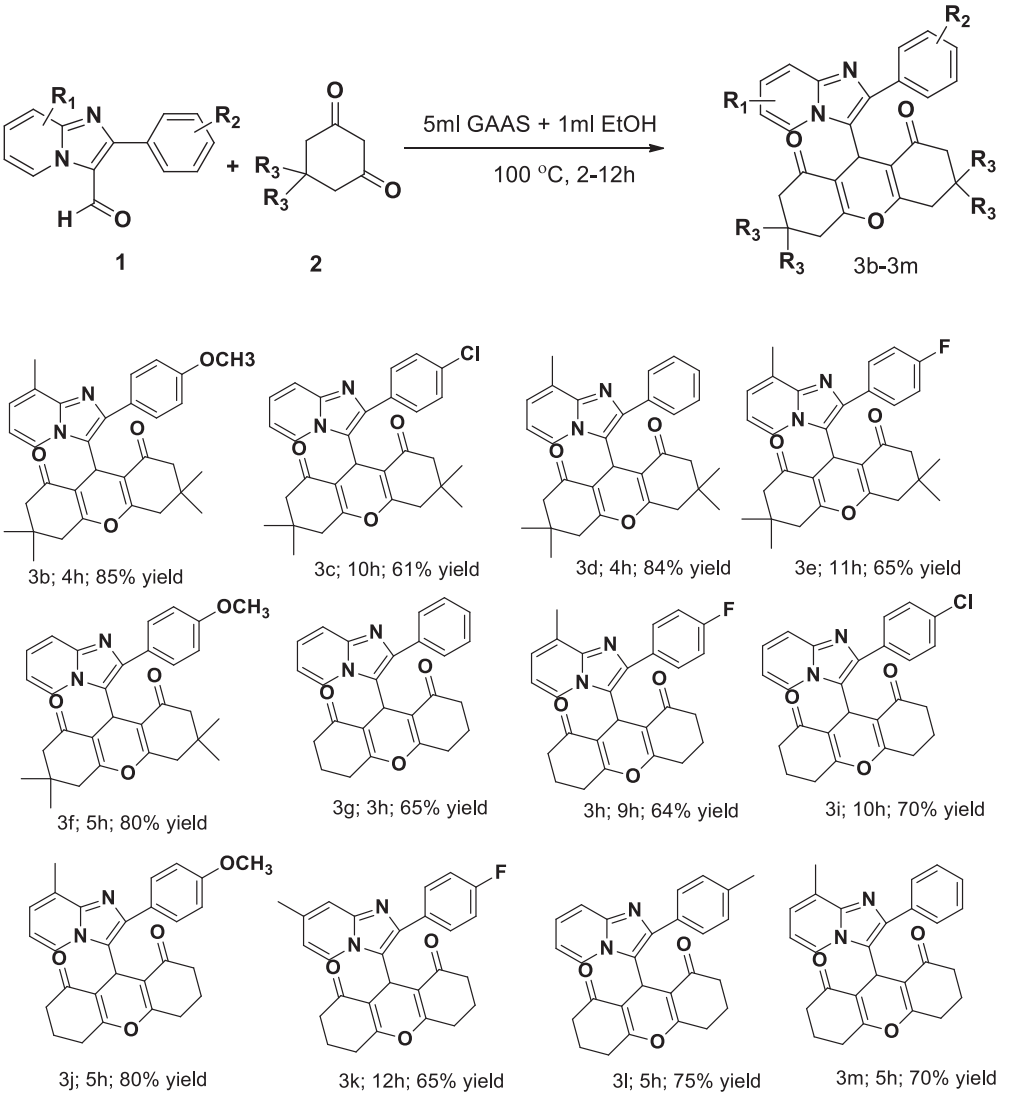
Figure 2. ORTEP diagram of 3 h (CCDC 1584692).

150 and 180 minutes. Eventually, GAAS can be recovered by concentrating water layer under reduced pressure using rotary evaporator. The recovered GAAS was further tested for its catalytic potential for the same reactions. The yield obtained in the recovered GAAS is given in Table 1. Furthermore, on scaling reactions upto 20 mmol, produced a product in almost no significant difference in the yield, indicating an effective methodology for practical synthesis of target molecules.

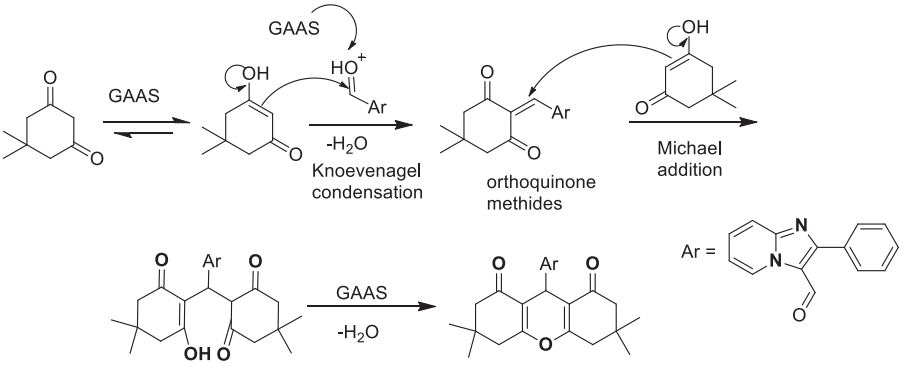
The reaction mechanism of product formation as depicted in Scheme 2 involved two name reactions knoevenagel condensation and Michael addition followed by cyclization and tautomerization.

All novel compounds (3a–3m) are stable white solids with a 61–88% yield. The photograph of compound 3 h is given in supporting information. Structures of compounds were established by spectroscopic techniques (MS, IR, ^{1}H NMR and ^{13}C NMR spectra). ^{1}H-NMR spectrum of 3a compound showed characteristic peaks at 5.03 ppm for CH proton as a singlet, 0.94–1.03 ppm for CH_3 proton as a singlet and 2.22–2.04 for CH_2 proton as a multiplet. ^{13}C-NMR spectrum showed characteristic peaks at 50.7 ppm for xanthenedione carbon linked with imidazopyridine nucleus and 197.2 ppm for carbonyl carbon. Additionally, the characteristic IR peaks at 1658 and 1624 cm^{-1} for C=O stretching for ketone functionality at the xanthenedione nucleus, 1192–1138 cm^{-1} for C–O stretching for ether at the pyran nucleus, 2952 and 2871 cm^{-1} for C–H stretching of methyl substitutent at the xanthenedione nucleus and 1353 cm^{-1} for C–N stretching in the imidazopyridine nucleus were useful for predicting the synthesized compound 3a. Melting point of the compound 3a was found to be in the range of 214–216 °C.

Furthermore, 3 h compound was crystallized by using ethanol under slow evaporation and characterized it by single crystal X-ray diffraction study. The data showed a triclinic shape of the 3 h (Figure 2). The crystallography data (provided in the Supporting Information) indicated that the crystallized compound is $C_{27}H2_{23}$ FN_2O_3 . We observed that the two 6-membered carbon rings in the xanthene-1,8(2H)-dione group fused to



Scheme 1. Synthesis of novel fused imidazopyridine bearing xanthenedione.



Scheme 2. Proposed reaction mechanism of imidazopyridine fused xanthenedione synthesis.

the central pyran group are puckered with slightly distorted envelope conformations and the central pyran group is puckered in a slightly distorted boat conformation.

Conclusion

Synthesis of novel bisheterocyclic imidazopyridine bearing xanthenedione derivatives using gluconic acid aqueous solution has been developed via domino reactions. The reactions are completed within 2–12 h depending on the type of substitution. The protocol is green, easy to operate, cost-effective, and furnished product in very good yield. The mechanism of reaction involves the knoevenagel condensation followed by Michael addition along with cyclization and tautomerization steps.

General procedure for synthesis of 3a-3m (Scheme 1)

1,3-Cyclohexanedione/5,5-Dimethyl-1,3-cyclohexanedione (0.28 g, 2 mmol) was dissolved in ethanol:GAAS (1 ml:5ml GAAS). Then, 2-Phenyl–imidazo [1,2-a] pyridine-3-carbaldehyde (0.22 g, 1 mmol) was added to the reaction mixture. The reaction mixture was stirred at 100 °C. After completion of the reaction (the progress of the reaction was monitored by TLC using ethyl acetate:n-hexane as eluent), the reaction mixture was cooled and then filtered. After filtration, the crude product was washed with hexane and further purified by column chromatography wherever it was needed.

Spectroscopic data of 3a compound

3,3,6,6-tetramethyl-9-(2-phenylimidazo[1,2-α]pyridine-3-yl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8 (2H)-dione

White solid; Yield 90%; mp = 214–216 °C; FT-IR (cm^{-1}) 2952, 2871, 1658, 1624, 1353, 1192, 1138, ^{1}H-NMR ($CDCl_3$, 400 MHz): $\delta = 8.86$ (d, $J = 6.8$ Hz, 1 H, Ar), 7.56 (d, $J = 8.8$Hz, 1 H, Ar), 7.35 (s, 5H), 7.22 (t, $J = 7.2$Hz, 1 H, Ar), 6.96 (t, $J = 6.8$Hz, 1 H, Ar), 5.03 (s, 1 H, CH), 2.22–2.04 (m, 8H), 1.03 (s, 6H), 0.94 (s,6H); ^{13}C -NMR ($CDCl_3$, 100 MHz): δ = 197.2, 162.5, 144.4, 144.0, 136.3, 129.5, 127.9, 127.6, 125.6, 124.6, 123.2, 116.9, 113.4, 111.7, 50.7, 40.8, 31.9, 29.1, 27.9, 22.6; MS-ESI $(M + H)^+$: 467.4 Found 467.4. HRMS(*m/z*): Calcd for $C_{30}H_{30}N_2O_3$ $(M + H)^+$: 467.2356, found 467.2351

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Supporting information

Full experimental detail, ESI-MS; HRMS, ^{1}H and ^{13}C NMR spectra of all compounds and XRD data of 3 h can be found via the "Supplementary Content" section of this article's webpage.

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